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CASE REPORT

Late reactivation of hepatitis B virus after rituximab-containing chemotherapy for mantle cell lymphoma: a case report

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Abstract

Background Hepatitis B virus (HBV) reactivation is commonly observed in HBsAg-positive hematologic patients undergoing immunosuppressive chemotherapy. Recent guidelines recommend antiviral prophylaxis to be continued for up to 12 months after the discontinuation of the anticancer regimen.

Case Presentation We report a case of a patient who underwent antiviral prophylaxis for 26 months after the discontinuation of a rituximab-containing chemotherapy regimen for a lymphoma and was admitted in the infectious diseases department with a 3-day history of jaundice, itching, and dark urine. After excluding other possible causes of acute liver damage, HBV reactivation was suspected. HBV-DNA was 4497000 IU/mL. Following reintroduction of entecavir, we observed a steady decline of ALT, AST, bilirubin and HBV-DNA serum levels, with a rapid resolution of acute hepatitis and an improvement in clinical conditions; one year after the event of HBV reactivation and beginning of antiviral therapy, the patient was virologically suppressed.

Discussion Our study demonstrates that the risk of HBV reactivation in HBsAg-positive patients with undetectable HBV-DNA can occur even after three years from the last administration of rituximab and several months after the withdrawal of prophylactic antiviral therapy in patients with hematological malignancies. This implies that a close monitoring of HBV-related markers including HBV-DNA must continue after the withdrawal of prophylactic NA therapy.

Keywords Hepatitis B · Lymphoma · Entecavir · Rituximab

Background

Hepatitis B virus (HBV) reactivation is a well-known complication of patients undergoing chemotherapy or immunosuppressive therapy for hematologic malignancies, particularly in the event of stem cell transplantation or when using monoclonal antibodies against the protein CD20 found on the surface of immune system B cells, such as rituximab. According to recent guidelines, there are two possible scenarios, leading to HBV reactivation. The first occurs in HBsAg carriers, who can be distinguished in active (serum HBV–DNA above 2000 IU/mL) or inactive (serum HBV–DNA lower than 2000 IU/mL or undetectable) [1, 2]. These patients have a higher risk of reactivation compared to non-carriers, and the diagnosis is based on the rise of serum HBV–DNA levels. The second scenario occurs in patients with resolved HBV infection (anti-HBc positive), in whom we can detect HBV–DNA as well as a HBsAg seroreversion during the reactivation; among this second group, a distinction must be made between patients with both anti-HBc and anti-HBs, who show a lower risk of reactivation, and anti-HBc positive patients without detectable anti-HBs, whose level of risk seems to be higher [3, 4].

While guidelines do not present a clear consensus regarding the management of patients with resolved HBV infection undergoing immunosuppressive treatments, HBV reactivation in inactive HBsAg carriers is well documented and must be prevented: in fact, both American and Italian guidelines [1, 5] suggest that antiviral prophylaxis is necessary in these patients undergoing immunosuppressive chemotherapy and

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that should be continued for 6–12 months after the discontinuation of the immunosuppressive regimen.

We report a case of late reactivation of HBV in a patient who took antiviral prophylaxis for 24 months after the discontinuation of a rituximab-containing chemotherapy regimen for a mantle cell lymphoma.

Case report

A 63-year-old man was diagnosed in 2011 with mantle cell lymphoma; the patient reported past HBV infection and blood tests were positive for HBsAg, anti-HBc and anti-HBe with undetectable serum HBV–DNA levels. Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were persistently normal and there were no hematochemical and liver ultrasound findings indicative of chronic active hepatitis. He was treated with eight cycles of R-CHOP (rituximab, cyclophosphamide, vincristine, adriamycin and prednisolone) with periodic administrations of rituximab alone during the following 24 months achieving complete remission of mantle cell lymphoma. According to the current guidelines, the patient received antiviral prophylaxis with entecavir (one tablet of 0.5 mg per day). He completed the immunosuppressive therapy in March 2014 but continued entecavir for 26 months after discontinuation of rituximab; since the patient remained negative for HBV–DNA, antiviral prophylaxis was then stopped in June 2016. We continued measuring ALT/AST and HBV–DNA levels at each outpatient periodic visit.

In April 2017, about 3 years after completing chemotherapy, he was admitted to the infectious diseases department with a 3-day history of jaundice, itching and dark urine. No abdominal pain, fever, weight loss, night sweats, nausea or vomiting were reported. Physical examination was unremarkable except for icteric skin and sclera. Laboratory data revealed increased serum level of AST and ALT [999 IU/L and 2126 IU/L, respectively (normal range (NR): 7–45)], gamma-glutamyl transpeptidase [240 IU/L (NR: 8–61)], total bilirubin [15 mg/dL with a direct fraction of 10.9 mg/dL (NR: <1.2)] and International Normalized Ratio of 1.18.

Since in Rome there was an active outbreak of acute hepatitis A, the patient was tested for specific IgG and IgM antibodies that resulted to be negative. Furthermore, hepatitis C, hepatitis E, hepatitis Delta, Human Immunodeficiency Virus (HIV) 1/2, Cytomegalovirus, Epstein Barr, and Herpes Symplex viruses serologies also tested negative. Abdomen ultrasound showed a slightly enlarged liver (longitudinal diameter 17.5 cm) without any sign of biliary tree dilatation. HBV-reactivation was suspected and serology markers showed HBsAg positive (> 1000 S/CO), HBeAg, anti HBe and anti HBc also were positive; HBV–DNA was 4,497,000 IU/mL.

Antiviral therapy was immediately started with entecavir 0.5 mg orally per day, with a rapid improvement of the clinical conditions and a reduction of transaminases and total bilirubin.

He was discharged in good clinical conditions and continued clinical follow-up as an outpatient. On May 22, blood tests showed AST 22 IU/L, ALT 31 IU/L, HBV–DNA 4.540 IU/ml. On January 15, 2018, HBV–DNA was 77 IU/mL (Fig. 1). A new abdomen ultrasonography was performed and showed findings similar to the previous one. On May 2018 the HBV–DNA serum assay resulted to be negative (< 20 IU/ml), whereas the liver function tests, including serum transaminases, were all within the normal range.

As of now, the patient is still undergoing regular follow-up while continuing therapy with entecavir.

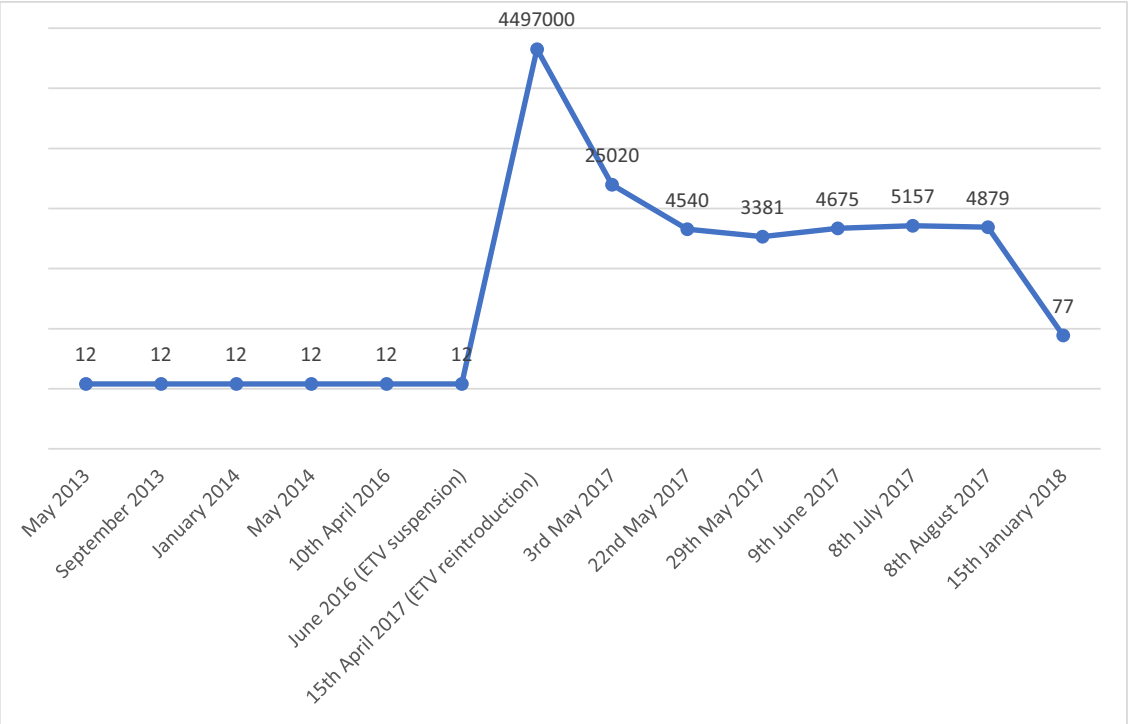
Discussion

HBV reactivation is commonly observed in HBsAg-positive patients undergoing immunosuppressive anticancer therapy; in particular, targeted therapies with monoclonal antibodies and rituximab-containing chemotherapy in haematologic malignancies have been recognized as risk factors for HBV reactivation among both active and inactive HBsAg carriers.

The cytotoxic effect caused by steroids, as well as chemotherapy on proliferative cells, leads to immunosuppression, representing the main risk factor for HBV reactivation in patients undergoing therapy for either haematologic or solid tumors [6]. The ensuing escape of HBV from immune surveillance leads to viral replication in hepatocytes. The advent of more recent monoclonal antibodies with profound and long-lasting immunosuppressive effects, such as anti-CD20 agents (i.e. rituximab), has led to the observation of cases of viral reactivation not only in chronic HBV carriers, but also in HBsAg-negative patients with serological markers of resolved HBV infection. Once the immunosuppressive therapy is stopped, a rebound immune response causes massive hepatocyte destruction that manifests with a raise in liver enzymes.

It is worth noting that rituximab has been observed to have long-lasting effects on both B cell and T cell depletion, with a very rapid decrease in both mature B cells and pre-B cells and a late effect on peripheral blood T cells, particularly CD4+ cells [7]. In our case, at admission, a complete peripheral blood lymphocyte typing showed no abnormalities.

The current guidelines [1, 5, 8] and expert opinions [9] recommend that patients defined as HBV inactive carriers (HBsAg-positive with undetectable HBV–DNA) must start pre-emptive prophylaxis with an antiviral agent at the moment of immunosuppressive therapy beginning. The use of lamivudine or a second-generation nucleos(t)ide analog



All values expressed in IU/ml, determined via Real Time-PCR. HBV: Hepatitis B Virus; ETV: Entecavir.

Fig. 1 Patient's HBV–DNA levels in time

(NA), such as entecavir or tenofovir, as the antiviral agent of choice is controversial: the use of prophylactic lamivudine, as reported by Yao et al. [3], might be feasible and cost/effective; however, its use is burdened by the high incidence of resistance mutations limiting its long-term efficacy [10]; furthermore, different studies show a higher incidence of HBV reactivation in patients taking lamivudine compared with prophylactic entecavir [11, 12]. Therefore, the use of a high-genetic barrier NA should be preferred, and the current European guidelines recommend entecavir, tenofovir disoproxil and tenofovir alafenamide as the drugs of choice [8].

The optimal duration of prophylactic therapy with NA has yet to be established. According to 2017 EASL guidelines [8] prophylaxis should continue for at least 12 months after cessation of the immunosuppressive treatment and discontinued only if the underlying disease is in remission. In patients undergoing rituximab-based chemotherapy, a longer duration of prophylaxis (up to 18 months after NA cessation) may be advisable [13]. Liver function tests and HBV–DNA should be monitored routinely during and after chemotherapy and for at least 12 months after withdrawal of the antiviral agent, as a large proportion of HBV reactivations develops after NA discontinuation [14].

In our patient, HBV reactivation developed 36 months after the last rituximab administration; to the best of our knowledge, the most delayed case reported in the literature of HBV reactivation after stopping rituximab-containing chemotherapy occurred at 32 months [15].

Following reintroduction of entecavir, we observed a steady decline of ALT, AST, bilirubin and HBV–DNA serum levels, with a rapid resolution of acute hepatitis and an improvement in clinical conditions; 1 year after the event of HBV reactivation and beginning of antiviral therapy, the patient results to be virologically suppressed with undetectable serum HBV–DNA and then must be considered an optimal responder.

In summary, the present case report demonstrates that the risk of HBV reactivation in HBsAg-positive patients with undetectable HBV–DNA can occur even after 3 years from the last administration of rituximab and 10 months after the withdrawal of prophylactic antiviral therapy in patients with hematological malignancies. This implies that a close monitoring of HBV-related markers including HBV–DNA must continue after the withdrawal of prophylactic NA therapy. Furthermore, this case raises the question of prolonging the NA administration in HBsAg positive patients beyond the recommended 12–18 months after cessation of deeply immunosuppressive regimens.

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Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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